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(54) Title: 5-HYDROXYTRYPTAMINE TRANSPORTER GENE POLYMORPHISMS

(57) Abstract: A method of determining the susceptibility of a human patient to gastrointestinal diseases such as IBS is disclosed. The method comprises detecting polymorphisms in genes encoding the 5-hydroxytryptamine transporter. Kits for carrying out such methods and methods of medical treatment of human patients are also disclosed

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/15004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

MEDLINE, BIOSIS, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/61039 A (GLAXO GROUP LTD ; KONG NING STEVEN (US); MANASCO PENELOPE K (US); M) 23 August 2001 (2001-08-23) page 6, line 14 - line 20 page 10, line 14 -page 11, line 4 page 18, line 17 -page 20	9-16
Y	—	17
Y	TATE C G: "Baculovirus-mediated expression of neurotransmitter transporters." METHODS IN ENZYMOLOGY. UNITED STATES 1998, vol. 296, 1998, pages 443-455, XP001181166 ISSN: 0076-6879 *the whole document, in particular page 444, first paragraph*	17
	—/—	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/15004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LESCH KLAUS-PETER ET AL: "Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region" SCIENCE (WASHINGTON D C), vol. 274, no. 5292, 1996, pages 1527-1531, XP001181144 ISSN: 0036-8075 cited in the application page 1527, column 3 page 1530, column 3, notes 11 and 14 -----	13, 15, 16
X	PATA CENGIZ ET AL: "Serotonin transporter gene polymorphism in irritable bowel syndrome" AMERICAN JOURNAL OF GASTROENTEROLOGY, vol. 97, no. 7, July 2002 (2002-07), pages 1780-1784, XP002279454 ISSN: 0002-9270 abstract page 1780, column 1 page 1781, column 1, paragraphs 2,5	13, 15, 16, 18
Y A	-----	17 1-8
A	WO 02/057306 A (BARDEN JULIAN ALEXANDER ; INTREAT PTY LTD (AU); GIDLEY-BAIRD ANGUS) 25 July 2002 (2002-07-25) claim 26 -----	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/15004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-9 because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: 9-11, 13-17 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 1-8 relate to a method of determining the susceptibility to gastrointestinal diseases in an individual, wherein said method is preferably carried out *in vivo* (page 11, lines 10-12 of the description) and amount thus a diagnostic method of practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 1-9

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 9-11, 13-17

1) Claim 10 relates to the use of a "ligand" for the manufacture of a medicament for treating a patient, wherein the "ligand" is only defined in terms of its function, namely that it is a "5HT ligand". This functional feature is however not sufficient to characterize said "ligand" so as to allow the skilled person to clearly and unambiguously understand the scope of said claim (Article 6 PCT).

A meaningful search over the whole claimed scope is therefore impossible and the search has been carried out for those part of the claims which appear clear in view of the description, namely those parts relating to the "5HT ligands" listed on page 16, line 28 to page 17, line 11 of the present description.

The search of claim 11, which is dependent on claim 10, was carried out accordingly.

Similarly, the search of claim 9, which relates to a method of treating a patient by administering such "5HT ligand", has also been carried out accordingly.

2) Claim 13 relates to a probe, primer or antibody only defined in term of its function, namely that it is capable of detecting a polymorphism as defined in claim 2 or 3 (i.e. a gastrointestinal disease susceptibility polymorphism, or a polymorphism which is in linkage disequilibrium with

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

such a polymorphism, in the 5-HTT gene/protein). This functional feature is however not sufficient to clearly characterize said probe, primer or antibody (Article 6 PCT). Indeed, a primer capable of detecting a polymorphism in the 5-HTT gene region could be outside of the 5-HTT gene sequence. A meaningful search over the whole claimed scope is therefore impossible and the search has been carried out for those parts of the claims which appear clear in view of the description, namely those parts relating to a PCR primer/probe consisting of the sequence GGCGTTGCCGCTCTGAATGC or GTGGTTGTCCAGTCAGTCCTC (underlined sequences of SEQ ID NOs: 1 or 2, page 18); to a probe of at least 10 nucleotides in length and having a sequence comprised in SEQ ID NO: 1 or SEQ ID NO: 2 (example 1, page 18 and page 8, lines 6-7, 20) and to antibody specific of the 5'-HTT protein (page 13, lines 15-16 and page 12, lines 22-28).

3) A lack of clarity in the sense of Article 6 PCT arises from the wrong back reference to claim 11 in claim 14.

Claim 14 relates to a kit for diagnosing susceptibility to gastrointestinal disease, comprising an agent, probe, primer or antibody as defined in claim 11. Claim 11, however, does not relate to any agent, probe, primer or antibody.

Taking into account the fact that the term "agent" has no precise meaning in the context of claim 14 and that said term is not defined in the present application, claim 14 has been interpreted as relating to a kit for diagnosing susceptibility to gastrointestinal disease comprising a probe, primer or antibody as defined in claim 13 as the only claim relating to a probe, antibody or primer is claim 13. The search of claim 14 has therefore been carried out accordingly (see item 2, above).

4) Claim 15 relates to an isolated polynucleotide or protein only defined in that it comprises "(i) a polymorphism that causes susceptibility to gastrointestinal disease or (ii) a naturally occurring polymorphism that is in linkage disequilibrium with (i)". These functional features are however not sufficient to clearly and unambiguously characterize said isolated polynucleotide or protein. Claim 15 lacks therefore clarity within the meaning of Article 6 PCT so as to render a meaningful search of said claim impossible.

Consequently, the search of claim 15 has been carried out for those parts of the application which do appear clear, namely those parts relating to the isolated polynucleotide or protein as being the 5-HTT gene or the 5-HTT protein (page 12, lines 22-23), in particular to polynucleotides comprising the sequence of SEQ ID NO: 1, SEQ ID NO: 2 (example 1), GenBank Acc. Number X76753, GenBank Acc. Number U79746, GenBank Acc. Number X76758, GenBank Acc. Number X76762 (Table 1) and GenBank Acc. Number X76754 (page 5, lines 7-10).

The search of claims 16 and 17 which have a back reference to claim 15, has been carried out accordingly.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/15004

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
WO 0161039	A 23-08-2001	AU EP JP WO US	4315301 A 1255870 A2 2003528593 T 0161039 A2 2003124566 A1		27-08-2001 13-11-2002 30-09-2003 23-08-2001 03-07-2003
WO 02057306	A 25-07-2002	WO CA EP WO	02057306 A1 2434490 A1 1360203 A1 03020762 A1		25-07-2002 25-07-2002 12-11-2003 13-03-2003